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Intensive Brief Chemotherapy With Hematopoietic Growth Factors as Hematological Support and Adjuvant Radiotherapy Improve the Prognosis in Aggressive Malignant Lymphoma

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An intensive brief chemotherapy and radiotherapy regimen including high doses of cyclophosphamide (5 g/m²), etoposide (1 g/m²), epirubicin (180 mg/m²), and ifosfamide (5 g/m²) administered in a period of 30 days followed by involved field radiotherapy to sites of initial bulky disease was administered to 46 untreated patients with high-intermedium and high-risk malignant lymphoma. G- or GM-CSF were used as hematological support instead of bone marrow transplantation. All patients had more than 3 adverse prognostic factors at diagnosis.

Forty-one patients (89%) achieve complete response (33 after chemotherapy and 8 partial responses were converted to complete response after adjuvant radiotherapy). Actuarial failure-free survival at 3 years is 83% and 37 of all patients started on therapy remain alive and in first remission at a median of 24.3 months from completion of treatment. Nearly all patients developed granulocytopenia grade IV; only 13 episodes of bacterial infection were documented. Because hematological recovery was very short (mean 13.6 days) no death related treatment and opportunistic infections were observed. Other non-hematological toxicities were scarce and well tolerated. No decrease >10% was observed in the left ventricular ejection fraction. None have developed clinically evident congestion heart failure or other late side effects. These results showed that G- or GM-CSF can act as hematological support instead of bone marrow transplantation during intensive and brief chemotherapy. These regimens produce higher complete remission rate, and adjuvant radiotherapy will improve the outcome in patients with bulky disease.

Key words: malignant lymphoma, bone marrow transplantation, hematopoietic growth factors, radiotherapy, epirubicin, etoposide, ifosfamide

INTRODUCTION

The development of curative combination chemotherapy for patients with advanced states of aggressive malignant lymphoma has been one of the major searches during the last years [1]. Initial reports of patients treated with combination chemotherapy with doxorubicin-based regimens were exciting. However, long-term results showed that only 30% of patients can be cured with this type of treatment [1]. Based on pilot studies it has been proposed that the prognosis of these patients would be improved by using second- or third-generation chemotherapeutic regimens containing non-cross-resistant agents designed to optimize dose intensity. However, the randomised clinical trials do not confirm these results [2].

Dose intensity has been reported to be important for cure [3,4]. Nevertheless, attempts to increase the proportion of responses and duration of remission have failed, so far, in randomized trials [5–8]. Failures have been

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attributed to modifications on original schedules to reduce side effects [9]. Use of hematopoietic growth factors, granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF), has been demonstrated to be useful in reducing the incidence and severity of myelosuppression, although results on duration of remission and survival have been controversial [10–13].

One of the most important advances has been the identification of prognostic groups in patients with malignant lymphoma based on the presence of prognostic factors [14]. Bulky disease remains one of the most important adverse prognostic factors because response is very slow in anatomical sites with bulky disease with prolongation of chemotherapy and development of resistant disease. Also, relapses are most frequent in these sites. For this reason combined therapy to treat patients with bulky disease even in patients with advanced stages has been proposed to be useful [15]. For this reason we began a prospective open study to explore further the importance of chemotherapeutic dose intensity in the treatment of patients with poor prognosis malignant lymphoma. We designed a novel regimen using augmented, but subtransplantation doses of single agents rather than multiple and small doses of the best single agents in the treatment of malignant lymphoma. Radiation therapy was employed in patients with bulky disease in an attempt to eradicate tumoral cells of these sites. G-CSF or GM-CSF were used to ameliorate the expected severe myelosuppression as previously has been demonstrated [16,17].

We employed cyclophosphamide, etoposide, epirubicin, and ifosfamide because these drugs had been very effective in malignant lymphoma. Also, toxicity is essentially against bone marrow and the use of growth factors was expected to avoid these side effects. Epirubicin is an anthracycline with low-cardiotoxicity, even in higher doses.

PATIENTS AND METHODS

All patients with intermediate- and high-grade malignant lymphoma presenting to the Oncology Hospital, National Medical Center between June 1992 to December 1993 were considered candidates for entry into this protocol. Criteria for eligibility were (as follow-up): a histological diagnosis of intermediate- and high-grade malignant lymphoma (excluding lymphoblastic lymphoma) according to the Working Formulation [18], age 18 to 65 years old, stage III or IV disease, and high- or high-intermedium risk, according to the International Risk Classification Project [14]. Patients were excluded if they were previously treated and had positive testing for acquired immunodeficiency syndrome or impaired renal, cardiac, hepatic, or bone marrow function, unless directly attributable to lymphoma involvement.

Pretreatment evaluation included a thorough history and physical examination, determination of performance status by Eastern Cooperative Oncology Group (ECOG), complete blood count and differential, serum chemistry including lactic dehydrogenase (LDH) (normal values less than 275 UI/L) and beta 2 microglobulin (normal values less than 3.5 μg/mL), and tests for hepatic and renal function. Cardiac function was monitored by left ejection ventricular fraction (LEVF) taken before and after treatment was administered. Evaluation chest radiograph also included computed tomograph (CT) scan of chest, abdomen, and pelvis, and bone marrow aspiration and biopsy.

Following treatment, restaging included repetition of all studies abnormal at diagnosis, including biopsy of clinically suspicious areas. This study was approved by the Institutional Review Board and all patients signed informed consent forms before entering the study.

Therapy consisted of:

1. Cyclophosphamide, 5 g/m^2, intravenous infusion (iv) on day 1. Diuresis was maintained to more than 60 ml/hr with saline solution and in some cases with furosemide administration. GM-CSF or G-CSF, 5 μg/kg/day, subcutaneously daily was started on day 2 until hematological recovery (granulocytes $>1.8 \times 10^9$/L, and platelets $>150 \times 10^9$/L). Hematopoietic growth factors were stopped 2 to 5 days before the following dose of chemotherapy.
2. Etoposide, 1 g/m^2, on saline solution (0.8 mg/mL) was planned to be administered on day 14, if granulocytes and platelets were normal. Again, GM-CSF or G-CSF on the same schedule were administered beginning on day 15 until hematological recovery (granulocytes $>1.8 \times 10^9$/L and platelets $>150 \times 10^9$/L). Newly hematopoietic growth factors were stopped 3 to 5 days before the following phase of chemotherapy.
3. Finally, the third phase was planned to be administered on day 29: epirubicin 180 mg/m^2, iv, diluted in 500 mL of saline solution, and ifosfamide 5 g/m^2, iv, diluted in 1,000 mL of saline solution. Mesna, 5 g/m^2, was administered diluted in 1,000 mL of saline solution and administered at the same time, as ifosfamide. GM-CSF or G-CSF as newly initiated on day 30 until normal values of granulocytes and platelets.

Trimethroprin with sulfamethoxazol and fluconazole were prophylactically administered from day 1 to 60. The patient was hospitalized to receive only the cyclophosphamide treatment or presence of secondary effects on complications due to chemotherapy. The rest of the treatment was administered on an outpatient basis. After the chemotherapy was administered if the patient had initial bulky disease defined as a mass >10 cm diameter or residual radiographic abnormalities (usually in CT scans) and was

consider partially responsive, they were treated with adjuvant radiotherapy as follows: treatment to the abdomen was delivered through anterior and posterior fields extended from the dome of the diaphragm to the iliac crest. The overall dose to the upper abdomen was limited to 2,000 cGy in 20 fractions over 4 weeks. The kidneys were shielded posteriorly with two half value layers of lead to reduce their dose to approximately 1,800 cGy. Regions of bulky disease received an additional boost of up to 2,000 cGy. Total doses to sites of bulky disease were 4,000 cGy.

Other sites of initial bulky disease were treated with involved fields which were limited to the affected lymph node bearing regions of any larger masses with doses of 4,000 cGy delivered in 4 weeks. The mantle was not used unless the mediastinum was involved. When it was necessary to treat the mediastinum, the tumor dose to the mediastinum was generally calculated in the mildplane of the upper mediastinum. The dose of the lower mediastinum was approximately 25% lower. The peripheral nodal area and the mildplane of the mediastinum were treated with a tumor dose of 4,000 cGy in 20 fractions over 4 weeks through parallel opposed anterior and posterior fields. Complete response (CR) was defined as the disappearance of all clinical evidence of disease and normalization of radiographs and relevant laboratory data that had been abnormal before therapy. To qualify as a CR there could be no evidence of relapse for at least 6 months. Partial response signifies a greater than 50% reduction of all clinically measurable disease for at least 4 months following completion of therapy. Patients with partial response and residual masses on CT scans who received adjuvant radiotherapy and had evidence of reduction of tumor mass without evidence of relapse for at least 6 months were considered converted to CR. Failure was defined when the reduction of tumor mass was less than 50% or new lesions were present during treatment.

Failure-free survival (FFS) was calculated to the beginning of therapy to the date of relapse. Survival was considered from the patients' entry to the study until death secondary to tumor progression or related to treatment.

Survival and FFS curves were calculated according to the method of Kaplan and Meier [19]. Because all patients had adverse prognostic factors and were in high or high-intermedium clinical risk, analyses to determine the influence on remission or survival were not performed. Toxicity was evaluated according to the World Health Organization criteria.

RESULTS

Forty-six patients were considered candidates for the study. Clinical characteristics can be seen in Table I. As previously mentioned all had adverse prognostic factors and advanced disease.

TABLE I. Patient Characteristics

Number	46
Sex	
Male	28
Female	18
Age (years)	
Median	48
Range	23–65
Histologic subtypes	
Diffuse large cell	30
Immunoblastic	5
Diffuse mixed	5
Anaplastic Kyl+	3
Small non-cleaved	3
Stage	
IV A	4
IV B	42
Clinical risk	
High	39
High-intermedium	7
Bulky disease	33
Lactic dehydrogenase >2 levels	43
Beta 2 microglobulin >2 levels	40
Extranodal involvement[a]	46
Bone marrow	28
Liver	23
Lung	7
Bone	1
Soft tissue	11

[a]Patients can have two or more extranodal anatomic sites involved.

Thirty-three out of 46 patients (71%) (95% confidence interval [CI] 60 to 83%) achieved a CR and 10 patients (21%) achieved a partial response. Thus overall response was observed in 43 out of 46 patients (92%) (95% CI 69 to 94%). Three patients had progressive disease and were considered failures. All died between 5 to 8 months after diagnosis and all were refractory to other salvage attempts.

The 10 patients with partial response received adjuvant radiotherapy and eight were converted to CR, thus a CR was achieved in 41 out of 46 patients (89%) (95% CI 70 to 91%). The two patients with no changes in CT scans were observed with no other treatment. Both had evidence of tumor progression 2 and 4 months after therapy and died secondary to lymphoma progression. All patients with PR has previous bulky disease at diagnosis. Twenty-three patients of the 33 patients with CR received adjuvant radiotherapy as planned because they initially had bulky disease. The 10 patients without bulky disease at diagnosis achieved CR and they did not receive adjuvant radiotherapy.

After a median follow-up of 24.3 months, thirty-seven (83%) patients remain in CR. Figure 1 shows the actuarial FFS, median has not been reached yet. Only 5 patients have relapsed and all relapses occurred at the initial sites

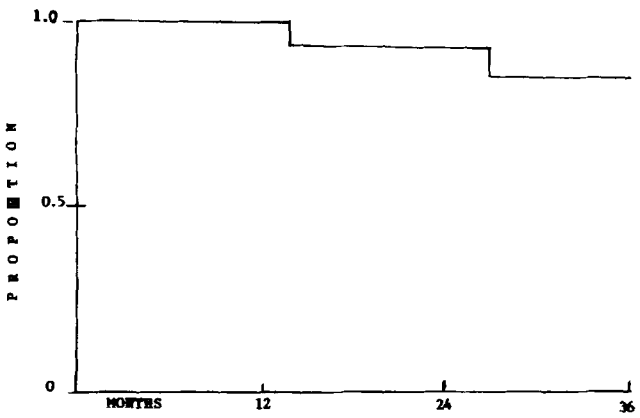

Fig. 1. Actuarial curve of failure free survival.

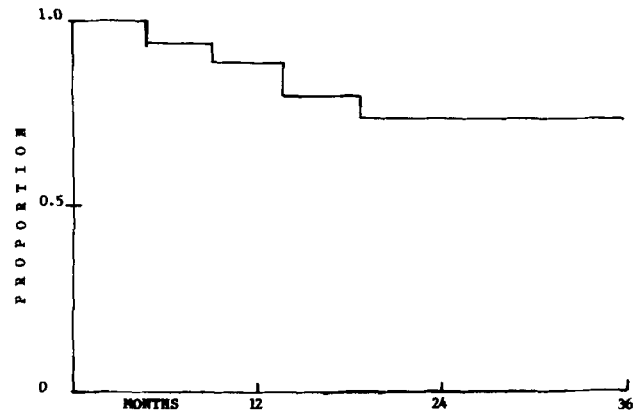

Fig. 2. Actuarial curve of overall survival.

of disease. Of these cases three patients received adjuvant radiotherapy and two did not. Of the 3 patients who received adjuvant radiotherapy, two were without initial bulky disease and one had bulky disease.

Figure 2 shows the actuarial overall survival, median has not been reached yet and 74% of the initial 46 cases are alive, free of disease.

Table II shows the hematological toxicity. As previously reported [16,17], with the use of similar regimens in refractory disease, severe granulocytopenia ($<0.1 \times 10^9$/L) was observed in all cases. However, the use of GM-CSF and G-CSF ameliorate the side effects. Days with severe granulocytopenia were shorter and hematological recovery was observed after a mean of 13.6 days. Although infection related granulocytopenia was observed in 15 out 138 cycles of chemotherapy (15%) (ten pneumonias and five septicemias) no death secondary to myelosuppression was observed because the periods of severe granulocytopenia were shorter. As expected, severe thrombocytopenia was not observed (the mean of platelet count as 78.6×10^9/L) and platelet transfusions were not necessary. Also, opportunistic infections were not observed.

As anticipated clinical cardiotoxicity was unusual. One patient developed transient tachycardia. LEVF taken after treatment and 6 and 18 months later did not show any statistical differences with baseline studies. No patients developed a decrease in abnormal values of LEVF (<45%).

The most non-hematological toxicity encountered was nausea and vomiting; however in most cases it was grade I or II and ondasentron was sufficient to control it. No death related treatment was recorded. Radiotherapy was well tolerated. Ten patients developed transient nausea and vomiting during abdomen treatment.

DISCUSSION

The treatment of advanced malignant lymphoma and poor prognostic factors remains unsatisfactory. The probability of CR in patients with clinical high-risk remains below 60% and the cure rate is less than 10%. In previous reports in patients with clinical high risk we reported a CR rate of 35 and 42%, and only 7 and 11% are alive free of disease at more than 5 years [20,21].

The presence of adverse prognostic factors has been emphasized in most trials, and patients with bulky disease, high levels of LDH, and beta 2 microglobulin are considered candidates for innovative regimens. Intensive chemotherapy with increasing doses of cytotoxic drugs has been tested. Shipp et al. [22] treated 18 patients with increasing doses of cyclophosphamide and doxorubicin in a modified CHOP with acceptable hematological toxicity. However, 2 patients relapsed (15%) and follow-up is too short [22]. Gianni et al. [23] in a prospective randomized trial compared high-sequential doses (HSD) of cyclophosphamide, metotrexate, and VP-16, followed (in the initial phase of the programm) by high doses of L-PAM and total body irradiation (TBI) with autologous bone marrow transplantation as hematological support compared to MACOP-B regimen. They reported a high toxic death rate (16%) and eliminated TBI and diminished the dose of L-PAM. The CR rate and FFS were better in the patients treated with HSD compared to MACOP-B treated patients. However, the initial high toxic death rate did not demonstrate any difference in overall survival [23]. The results of these studies can be compared to our results, using a different therapeutic approach, but with the same hypothesis: a high dose of chemotherapy can more quickly eliminate the possibility of resistant tumoral cells and the use of adjuvant radiotherapy can consolidate the CR with chemotherapy.

Haouin et al. [24] recently reported the results of a large randomized clinical trial comparing the use of consolidation phase with non-cross-resistant drugs in patients in CR after the administration of LNH-84 protocol to

TABLE II. Hematological Toxicity

	Cyclophosphamide	Etoposide (days)	Epirubicin/ifosfamide
Granulocyte counts			
$<0.1 \times 10^9$/L			
Median	4.6	6.5	6.9
Range	3–9	3–10	5–15
$<1.0 \times 10^9$/L			
Median	6.9	8.0	7.5
Range	4–10	6–14	6–18
$>1.8 \times 10^9$/L			
Median	12.0	13.8	15.8
Range	10–18	12–18	13–22
Delays in treatment (mean)	0	2	3
Infection n/n (%)	4/46 (8)	5/46 (10)	6/46 (13)
Death related granulocytopenia	0	0	0

high dose chemotherapy and autologous bone marrow transplantation as hematological support. The results did not show any statistical difference in duration of CR and overall survival [24]. Verdonck et al. [25] treated patients with slow response after three cycles of conventional CHOP either with intensive chemotherapy and autologous bone marrow transplantation or five cycles more of the same CHOP regimen. No differences were observed between the two arms in FFS and overall survival. However, in this study patients with low or intermediate-low clinical risk were the majority (56%) and comparison is difficult in clinical trials with patients with high-risk [25].

Our results can be compared to the studies of Shipp et al. [22] and Gianni et al. [23] because we tested the efficacy of intensive brief chemotherapy as first line of treatment in patients with advanced disease and high risk with the presence of adverse prognostic factors. The CR rate and overall survival are better than that reported previously with conventional chemotherapy [1]. The results of Verdonck et al. [25] can confirm the possibility with patients with slow response can develop drug resistance and the use of high doses of chemotherapy in a second step can be unsatisfactory.

Bulky disease has been considered an adverse prognostic factor in all patients with malignant lymphoma, including early stages. The use of radiotherapy in patients with early stage has been considered curative in most cases with overall survival >70% for patients in stage I and 50% in patients with stage II [26]. However, relapse is a constant feature in these cases and salvage chemotherapy has been reported to be less useful [27]. For this reason combined therapy has been considered as a possible therapeutic approach. Some retrospective studies with a small number of patients showed improvement in these patients [27]. Glick et al. [28] reported a randomized trial whose patients with early stage received either CHOP or CHOP plus adjuvant radiotherapy to sites of bulky disease (3,000 cGy). The FFS and overall survival were better in patients treated with combined therapy [28]. In advanced stages radiotherapy has been used only as a palliative [26]. In a previous study we demonstrate that adjuvant radiotherapy improves FFS and overall survival in patients with advanced stages and bulky disease treated with conventional chemotherapy [15].

Thus, for this reason we attempted to combine four of the most effective drugs in the treatment of malignant lymphoma administered in a short period of time to avoid the appearance of resistant disease and adjuvant radiotherapy in limited fields to sites with previous bulky disease or residual nodal postchemotherapy disease. Our results using a brief intensive regimen with high doses of cytotoxic drugs are very encouraging. Most patients responded rapidly during the induction phase and it has been demonstrated that rapid responders have better survival. The toxicity of this regimen was severe but no life-threatening complications were observed. The use of G-CSF or GM-CSF was sufficient to shorten the period of severe granulocytopenia and for this reason infection, although frequent, was not mortal.

Although chemotherapy was used in intensive doses, the use of hematopoietic growth factors limited the expected myelosuppression and was not resistant to treatment.

The use of intensive chemotherapy in patients with advanced malignant lymphoma and the presence of adverse prognostic factors appears to be the treatment of choice as first line treatment. More randomized studies are necessary to define the role of this therapeutic approach.

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